Claims

1. A method for in vitro production of regulatory T cells, comprising:

introducing an amount of hematopoietic progenitor cells and an amount of lymphoreticular stromal cells capable of mitosis into an open cell porous, solid matrix having interconnected pores of a pore size sufficient to permit the hematopoietic progenitor cells and the lymphoreticular stromal cells to grow in the matrix,

co-culturing the hematopoietic progenitor cells and the lymphoreticular stromal cells, and

isolating regulatory T cells from the cultured cells,

wherein the lymphoreticular stromal cells are derived from at least one lymphoid soft tissue selected from the group consisting of thymus, spleen, liver, lymph node, skin, tonsil, Peyer's patches and combinations thereof, and comprise one of more of fibroblasts, keratinocytes, epithelial cells, dendritic cells (DCs), and antigen presenting cells; and the amount of the lymphoreticular stromal cells is sufficient to support the growth and differentiation of the hematopoietic progenitor cells.

2. The method of claim 1, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are co-cultured in the presence of IL-7 and IL-15.

3. The method of claim 1, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are of human origin.

4. The method of claim 1, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are of murine origin.

5. The method of claim 1, wherein the regulatory T cells are isolated based on CD4+CD25+ phenotype.

6. The method of claim 1, wherein the regulatory T cells are isolated using fluorescent activated cell sorting, affinity column separation, affinity magnetic beads, affinity magnetic particles, complement-mediated lysis, panning, or tetrameric complex based separation.

7. The method of claim 1, wherein the hematopoietic progenitor cells are selected from the group consisting of pluripotent stem cells, multipotent progenitor cells and progenitor cells committed to specific hematopoietic lineages.

8. The method of claim 1, wherein the hematopoietic progenitor cells are derived from tissue selected from the group consisting of bone marrow, peripheral blood, mobilized peripheral blood, umbilical cord blood, placental blood, lymphoid soft tissue, fetal liver, embryonic cells and aortal-gonadal-mesonephros derived cells.

9. The method of claim 8, wherein the hematopoietic progenitor cells are derived from tissue selected from the group consisting of bone marrow, mobilized peripheral blood and umbilical cord blood.

10. The method of claim 1, wherein the lymphoreticular stromal cells are seeded prior to inoculating the hematopoietic progenitor cells.

11. The method of claim 1, wherein the porous solid matrix is an open cell porous matrix having a percent open space of at least 75%.

12. The method of claim 1, wherein the porous solid matrix is an open cell porous matrix having at least 80 pores per square inch (ppi).

13. The method of claim 11 or 12, wherein the porous solid matrix has pores defined by interconnecting ligaments having a diameter at midpoint, on average, of less than 150 μm.

14. The method of claim 1, wherein the porous, solid matrix having seeded hematopoietic progenitor cells and their progeny, and lymphoreticular stromal cells, is impregnated with a gelatinous agent that occupies pores of the matrix.

15. The method of claim 1, wherein the lymphoid soft tissue is selected from the group consisting of thymus and skin.

16. The method of claim 15, wherein the progenitor cells committed to specific hematopoietic lineages are committed to a T cell lineage.

17. The method of claim 1 or 15, wherein the hematopoietic progenitor cells are CD34+ cells.

18. The method of claim 1, wherein the progenitor cells are CD34+ cells, the lymphoreticular stromal cells are derived from skin, and the co-culture comprises IL-7 and IL-15.

19. The method of claim 3 or 18, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are autologous to a subject to be treated with the isolated regulatory T cells.

20. The method of claim 3 or 18, wherein the hematopoietic progenitor cells are allogeneic and the lymphoreticular stromal cells are autologous to a subject to be treated with the isolated regulatory T cells.

21. The method of claim 11 or 12, wherein the porous solid matrix is a metal-coated reticulated open cell foam of carbon containing material.

22. The method of claim 21, wherein the metal is selected from the group consisting of tantalum, titanium, platinum, niobium, hafnium, tungsten, and combinations thereof, and wherein said metal is coated with a biological agent selected from the group consisting of collagens, fibronectins, laminins, integrins, glycosaminoglycans, vitrogen, antibodies and fragments thereof, and combinations thereof.

23. The method of claim 22, wherein the metal is tantalum.

24. A method for producing a hematopoietic cell population depleted of regulatory T cells, comprising:

introducing an amount of hematopoietic progenitor cells and an amount of lymphoreticular stromal cells capable of mitosis into an open cell porous, solid matrix

having interconnected pores of a pore size sufficient to permit the hematopoietic progenitor cells and the lymphoreticular stromal cells to grow in the matrix,

co-culturing the hematopoietic progenitor cells and the lymphoreticular stromal cells, and

removing regulatory T cells from the cultured cells to produce a hematopoietic cell population depleted of regulatory T cells,

wherein the lymphoreticular stromal cells are derived from at least one lymphoid soft tissue selected from the group consisting of thymus, spleen, liver, lymph node, skin, tonsil, Peyer's patches and combinations thereof, and comprises one or more of fibroblasts, keratinocytes, epithelial cells, dendritic cells (DCs), and antigen presenting cells; and the amount of the lymphoreticular stromal cells is sufficient to support the growth and differentiation of the hematopoietic progenitor cells.

25. The method of claim 24, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are co-cultured in the presence of IL-7 and IL-15.

26. The method of claim 24, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are of human origin.

27. The method of claim 24, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are of murine origin.

28. The method of claim 24, wherein the regulatory T cells are removed based on CD4+CD25+ phenotype.

29. The method of claim 24, wherein the regulatory T cells are isolated using fluorescent activated cell sorting, affinity column separation, affinity magnetic beads, affinity magnetic particles, complement-mediated lysis, panning, or tetrameric complex based separation.

30. The method of claim 24, wherein the hematopoietic progenitor cells are selected from the group consisting of pluripotent stem cells, multipotent progenitor cells and progenitor cells committed to specific hematopoietic lineages.

31. The method of claim 24, wherein the hematopoietic progenitor cells are CD34+ cells.

32. The method of claim 24, wherein the hematopoietic progenitor cells are derived from tissue selected from the group consisting of bone marrow, peripheral blood, mobilized peripheral blood, umbilical cord blood, placental blood, lymphoid soft tissue, fetal liver, embryonic cells and aortal-gonadal-mesonephros derived cells.

33. The method of claim 32, wherein the hematopoietic progenitor cells are derived from tissue selected from the group consisting of bone marrow, mobilized peripheral blood and umbilical cord blood.

34. The method of claim 24, wherein the lymphoreticular stromal cells are seeded prior to inoculating the hematopoietic progenitor cells.

35. The method of claim 24, wherein the porous solid matrix is an open cell porous matrix having a percent open space of at least 75%.

36. The method of claim 24, wherein the porous solid matrix is an open cell porous matrix having at least 80 pores per square inch (ppi).

37. The method of claim 35 or 36, wherein the porous solid matrix has pores defined by interconnecting ligaments having a diameter at midpoint, on average, of less than 150 μm.

38. The method of claim 35 or 36, wherein the porous solid matrix is a metal-coated reticulated open cell foam of carbon containing material.

39. The method of claim 38, wherein the metal is selected from the group consisting of tantalum, titanium, platinum, niobium, hafnium, tungsten, and combinations thereof, and wherein said metal is coated with a biological agent selected from the group

consisting of collagens, fibronectins, laminins, integrins, glycosaminoglycans, vitrogen, antibodies and fragments thereof, and combinations thereof.

40. The method of claim 39, wherein the metal is tantalum.

41. The method of claim 24, wherein the porous, solid matrix having seeded hematopoietic progenitor cells and their progeny, and lymphoreticular stromal cells, is impregnated with a gelatinous agent that occupies pores of the matrix.

42. The method of claim 24, wherein the lymphoid soft tissue is selected from the group consisting of thymus and skin.

43. The method of claim 42, wherein the lymphoid soft tissue is skin and the lymphoreticular stromal cells comprise fibroblasts and keratinocytes.

44. The method of claim 42, wherein the progenitor cells committed to specific hematopoietic lineages are committed to a T cell lineage.

45. The method of claim 24 or 42, wherein the hematopoietic progenitor cells are CD34+ cells.

46. The method of claim 24, wherein the progenitor cells are CD34+ cells, the lymphoreticular stromal cells are derived from skin, and the co-culture comprises IL-7 and IL-15.

47. The method of claim 24 or 46, wherein the hematopoietic progenitor cells and the lymphoreticular stromal cells are autologous to a subject to be treated with the hematopoietic cell population depleted of regulatory T cells.

48. The method of claim 24 or 46, wherein the hematopoietic progenitor cells are allogeneic and the lymphoreticular stromal cells are autologous to a subject to be treated with the hematopoietic cell population depleted of regulatory T cells.

49. The method of claim 24, further comprising exposing the culture to antigen or antigen presenting cells.

50. The method of claim 24 or 34, further comprising isolating antigen-specific T cells from the hematopoietic cell population depleted of regulatory T cells.

51. A method for inhibiting an immune response, comprising administering to a subject in need thereof isolated regulatory T cells produced according to claim 1-22 or 23, in an amount effective to inhibit an immune response.

52. The method of claim 51, wherein the isolated regulatory T cells are administered systemically.

53. The method of claim 51, wherein the isolated regulatory T cells are administered locally to a site of inflammation.

54. The method of claim 51, wherein the subject has undergone or is undergoing a transplantation.

55. The method of claim 54, wherein the transplantation is a bone marrow transplantation.

56. The method of claim 54, wherein the transplantation is an organ transplantation.

57. The method of claim 51, wherein the subject has an inflammatory condition.

58. The method of claim 57, wherein the inflammatory condition is selected from the group consisting of non-autoimmune inflammatory bowel disease, post-surgical adhesions, coronary artery disease, hepatic fibrosis, acute respiratory distress syndrome, acute inflammatory pancreatitis, endoscopic retrograde cholangiopancreatography-induced pancreatitis, burns, atherogenesis of coronary, cerebral and peripheral arteries, appendicitis, cholecystitis, diverticulitis, visceral fibrotic disorders, wound healing, skin scarring

disorders (keloids, hidradenitis suppurativa), granulomatous disorders (sarcoidosis, primary biliary cirrhosis), asthma, pyoderma gandrenosum, Sweet's syndrome, Behcet's disease, primary sclerosing cholangitis, and an abscess.

59. The method of claim 57, wherein the inflammatory condition is an autoimmune condition.

60. The method of claim 59, wherein the autoimmune condition is selected from the group consisting of rheumatoid arthritis, rheumatic fever, ulcerative colitis, Crohn's disease, autoimmune inflammatory bowel disease, insulin-dependent diabetes mellitus, diabetes mellitus, juvenile diabetes, spontaneous autoimmune diabetes, gastritis, autoimmune atrophic gastritis, autoimmune hepatitis, thyroiditis, Hashimoto's thyroiditis, insulitis, oophoritis, orchitis, uveitis, phacogenic uveitis, multiple sclerosis, myasthenia gravis, primary myxoedema, thyrotoxicosis, pernicious anemia, autoimmune haemolytic anemia, Addison's disease, scleroderma, Goodpasture's syndrome, Guillain-Barre syndrome, Graves' disease, glomerulonephritis, psoriasis, pemphigus vulgaris, pemphigoid, sympathetic opthalmia, idiopathic thrombocylopenic purpura, idiopathic feucopenia, Siogren's syndrome, Wegener's granulomatosis, poly/dermatomyositis, and systemic lupus erythematosus.

61. The method of claim 51, wherein the subject has a microbial infection.

62. The method of claim 61, wherein the microbial infection is an RSV infection.

63. The method of claim 61, wherein the microbial infection results in sepsis.

64. The method of claim 51, wherein the subject has an allergy or is experiencing an allergic reaction.

65. The method of claim 51, wherein the subject is experiencing immune hypersensitivity.

66. The method of claim 51, wherein the subject has stromal keratitis.

67. The method of claim 51, wherein the subject is undergoing gene therapy.

68. The method of claim 51, wherein the subject is undergoing allograft rejection.

69. The method of claim 51, wherein the subject has atherosclerosis.

70. The method of claim 51, wherein the subject has myocarditis

71. The method of claim 51, wherein the progenitor cells and lymphoreticular stromal cells are autologous to the subject.

72. The method of claim 51, wherein the progenitor cells are allogeneic and the lymphoreticular stromal cells are autologous to the subject.

73. The method of claim 51, wherein the isolated regulatory T cells are administered to the subject repeatedly.

74. A method for increasing immune reactivity of a transplanted cell population, comprising

administering to a subject in need thereof a cell population depleted of regulatory T cells.

75. The method of claim 74, wherein the cell population depleted of regulatory T cells is the hematopoietic cell population depleted of regulatory T cells produced according to claim 24-49 or 50.

76. The method of claim 74, wherein the transplanted cell population is a hematopoietic cell population.

77. The method of claim 74, wherein the subject is undergoing cancer treatment.

78. The method of claim 74, wherein the transplanted cell population is a dendritic cell based vaccine or an antigen presenting cell based vaccine.

79. The method claim 74, wherein the transplanted cell population is an antigen-specific effector T cell population.

80. An isolated population of regulatory T cells produced by the method of claim 1-22 or 23.